eukaryotic cells to delete or make defective *MLH* genes, said eukaryotic cells being derived from yeast.

33. The process according to claim 23, wherein said eukaryotic cells are derived from plants.

34. The process according to claim 29, wherein said eukaryotic cells are *pms1* mutants or *msh2* mutants or *pms1 msh2* double mutants.

35. The process according to claim 23, wherein said eukaryotic cells are germ-line cells.

REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Claim 12 has been cancelled without prejudice, claims 11, 13, 16-18 and 22 have been amended, and new claims 23-35 have been added. The claim amendments and new claims have been presented to more particularly define the present invention and to put the claims in better form under U.S. practice. Support for the claim amendments and new claims is readily apparent from the teachings of the specification and the original claims.

Applicants wish to note that unless specifically recited in the arguments below, the changes to the claims are merely editorial in nature and should not be construed to narrow the scope of the claims.

With regard to the rejection of claims 11-13, 16, 17, 21 and 22 under 35 USC § 112, second paragraph, this rejection is deemed to be untenable in view of the cancellation of claim 12 and the amendment to the claims, and is thus respectfully traversed.

Claim 11 has been amended to clearly define how the method steps of the claim enable meiotic recombination *in vivo* of partially homologous DNA sequences having up to 30% of base mismatches. By genetically or physiologically manipulating eukaryotic cells comprising these partially homologous DNA sequences to render defective their enzymatic mismatch repair system, the presently claimed method allows the meiotic recombination *in vivo* of these partially homologous DNA sequences to occur.

Further, with regard to the Examiner's concerns over the lack of specific culturing conditions in the claims, Applicants believe that the Examiner's concerns are unjustified. It is not necessary under U.S. practice to set forth every minute detail of the present invention in the claims. It is only required under U.S. practice to set forth such details which enables one skilled in the art to practice the claimed invention without undue experimentation based on the teachings of the specification and the knowledge in the art. Thus, the step of *"culturing said manipulated eukaryotic cells under conditions to effect meiotic recombination in vivo of said partially homologous DNA sequences"* should not read in a vacuum, as the Examiner has done in this case, but in light of the teachings of the specification and the knowledge in the art.

It is well known to one skilled in the art how to culture "*eukaryotic cells under conditions to effect meiotic recombination*". Applicants will submit references to demonstrate such knowledge in the near future.

Applicants also note that the claims have been amended to clearly specify that the process of the present invention is limited to ***eukaryotic cells*** and not to whole animals which Applicants believe should alleviate many of the Examiner's 112 concerns.

With regard to claim 13, Applicants believe that each ground of rejection against this claim has been alleviated by the amendments to the claim. Specifically, claim 13 has been amended to more particularly define how the eukaryotic cells (*comprising said partially homologous DNA sequences*) of claim 11 are obtained (*mixing (a) a first group of eukaryotic cells comprising a first DNA sequence with (b) a second group of eukaryotic cells comprising a second DNA sequence which is partially homologous to said first DNA sequence and which has up to 30% base mismatches with said first DNA sequence, to form diploids*).

With regard to claims 16 and 17, Applicants have amended these claims to more particularly define how the enzymatic mismatch repair system of said eukaryotic cells are rendered defective (*by genetically or physiologically manipulating said eukaryotic cells to delete or make defective at least one eukaryotic homologue of mutS protein and/or at least one eukaryotic homologue of mutL protein*). Claim 17 is only directed to a more specific embodiment of claim 16. Thus, it is clear how the limitations of claims 16 and 17 relate to the process steps of claim 11.

Lastly, with regard to claim 22, Applicants have amended the preamble and the method steps of this claim to more clearly define the process of making eukaryotic cells of a hybrid

eukaryotic specie. Applicants believe that the claim is now clear as to the meaning of the term "hybrid". Further, with regard to the Examiner's concern as to how the eukaryotic cells of the hybrid eukaryotic specie are recovered, Applicants note that such recoveries of "hybrid" eukaryotic cells are well known to one skilled in the art and thus, no additional details beyond that which is stated in the claim, are necessary. Finally, Applicants also believe that the term "mixture" has sufficient antecedent basis since the previous method step teaches ***mixing*** (a) a first group of eukaryotic cells (*comprising a first DNA sequence and having a defective enzymatic mismatch repair system which is made defective by genetic or physiological manipulation*) with (b) a second group of eukaryotic cells (*comprising a second DNA sequence which is partially homologous to said first DNA sequence and which has up to 30% base mismatches with said first DNA sequence, and having a defective enzymatic mismatch repair system which is made defective by genetic or physiological manipulation*), to form diploids.

Thus, in view of amendments to the claims and the comments above, this rejection under 35 USC § 112, second paragraph, cannot be sustained and should be withdrawn.

With regard to the rejections of claims 11-13, 16, 17, 20 and 21 under 35 USC § 112, first paragraph, these rejections are deemed to be untenable in view the cancellation of claim 12 and the amendment to the claims, and is thus, respectfully traversed.

As stated earlier, Applicants have amended the claims to clearly specify that the process of the present invention is limited to ***eukaryotic cells*** and not to whole animals. Thus, Applicants believe that the new matter rejection under 35 USC § 112, first paragraph, should be withdrawn.

Further, based on the teachings of the specification and the knowledge in the art, a skilled artisan can clearly practice the claimed process and all of its method steps comprised therein. Applicants will be submit references demonstrating to the Examiner that the specification does provide sufficient guidance to one skilled in the art regarding (1) effecting meiotic recombination *in vivo* of partially homologous DNA sequences in eukarytic cells, (2) making hybrid eukaryotic cells and DNA sequences, (3) forming diploids, (4) obtaining eukarytic cells with defective enzymatic mismatch repair systems, or missing or containing defective at least one eukaryotic homologue of *mutS* protein and/or at least one eukaryotic homologue of *mutL* protein, and (5) using germ cells for *in vivo* meiotic recombination.

Thus, Applicants respectfully submit that these rejections will not be sustainable and should be withdrawn.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

In addition, to further assist the Examiner in reviewing the claims, Applicants have also submitted a paper containing all the pending claims in updated form. This paper is entitled "**Present Pending Claims Resulting from Preliminary Amendment**"

In view of the foregoing amendments and remarks, Applicants believe that the application is now in condition for allowance. Such action is thus respectfully solicited.

If, however, the Examiner has any suggestions for expediting the allowance of the application or believes that direct communication with Applicants' attorney will advance the

prosecution of this case, the Examiner is invited to contact the undersigned at the telephone number below.

Respectfully submitted,

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January 4, 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

11. (Amended) A process ~~for the~~of enabling meiotic recombination *in vivo* of partially homologous DNA sequences having up to 30% of base mismatches in eukaryotic cells, said process comprising

genetically or physiologically manipulating eukaryotic cells ~~containing~~comprising said partially homologous DNA sequences to render defective the enzymatic mismatch repair system of said eukaryotic cells; and

culturing said manipulated eukaryotic cells under conditions to ~~result in the~~effect meiotic recombination *in vivo* of said partially homologous DNA sequences.

~~12. The process according to claim 11, further comprising forming and/or isolating hybrid genes and their coded proteins.~~

13. (Amended) The process according to claim 11, wherein said eukaryotic cells comprising said partially homologous DNA sequences are ~~formed~~obtained by mixing (a) a first group of eukaryotic cells ~~containing~~comprising a first DNA sequence ~~and having a defective enzymatic mismatch repair system~~ with (b) a second group of eukaryotic cells ~~containing~~comprising a second DNA sequence which is partially homologous to said first DNA sequence ~~by having~~and which has up to 30% base mismatches with said first DNA sequence ~~and having a defective enzymatic mismatch repair system~~, to form diploids.

14. (Not Amended) The process according to claim 11, wherein said eukaryotic cells are derived from unicellular organisms.

15. (Not Amended) The process according to claim 14, wherein the unicellular organisms are yeasts.

16. (Amended) The process according to claim 11, wherein said ~~eukaryotic cells having said defective~~ enzymatic mismatch repair system ~~are missing or have~~of said eukaryotic cells are rendered defective by genetically or physiologically manipulating said eukaryotic cells to delete or make defective at least one eukaryotic homologue of *mutS* protein and/or at least one eukaryotic homologue of *mutL* protein.

17. (Amended) The process according to claim 16, wherein said enzymatic mismatch repair system of said eukaryotic cells ~~containing the partially homologous DNA sequences are missing or have~~are rendered defective by genetically or physiologically manipulating said eukaryotic cells to delete or make defective at least one eukaryotic homologue of *mutS* proteins.

18. (Amended) The process according to claim 11, wherein said enzymatic mismatch repair system of said eukaryotic cells ~~containing the partially homologous DNA sequences are missing or have~~are rendered defective by genetically or physiologically manipulated said eukaryotic cells to delete or make defective *MLH* genes, said eukaryotic cells being derived from yeast.

19. (Not Amended) The process according to claim 11, wherein said eukaryotic cells are derived from plants.

20. (Not Amended) The process according to claim 15, wherein said eukaryotic cells are *pms1* mutants or *msh2* mutants or *pms1 msh2* double mutants.

21. (Not Amended) The process according to claim 11, wherein said eukaryotic cells are germ-line cells.

22. (Amended) A process of making eukaryotic cells of a hybrid eukaryotic specie, said process comprising:

mixing (a) a first group of eukaryotic cells ~~containing~~(i) comprising a first DNA sequence and (ii) having a defective enzymatic mismatch repair system which is made defective by genetic or physiological manipulation, with (b) a second group of eukaryotic cells ~~containing~~(i) comprising a second DNA sequence which is partially homologous to said first DNA sequence ~~by having~~and which has up to 30% base mismatches with said first DNA sequence, and (ii) having a defective enzymatic mismatch repair system which is made defective by genetic or physiological manipulation, to form diploids,

culturing the mixture under conditions to ~~result in the~~effect meiotic recombination *in vivo* of said partially homologous first and second DNA sequences to make eukaryotic cells of said hybrid eukaryotic specie, and

recovering eukaryotic cells of said hybrid eukaryotic specie.

PRESENT PENDING CLAIMS RESULTING FROM PRELIMINARY AMENDMENT

11. (Amended) A process of enabling meiotic recombination *in vivo* of partially homologous DNA sequences having up to 30% of base mismatches in eukaryotic cells, said process comprising

genetically or physiologically manipulating eukaryotic cells comprising said partially homologous DNA sequences to render defective the enzymatic mismatch repair system of said eukaryotic cells, and

culturing said manipulated eukaryotic cells under conditions to effect meiotic recombination *in vivo* of said partially homologous DNA sequences.

13. (Amended) The process according to claim 11, wherein said eukaryotic cells comprising said partially homologous DNA sequences are obtained by mixing (a) a first group of eukaryotic cells comprising a first DNA sequence with (b) a second group of eukaryotic cells comprising a second DNA sequence which is partially homologous to said first DNA sequence and which has up to 30% base mismatches with said first DNA sequence, to form diploids.

14. The process according to claim 11, wherein said eukaryotic cells are derived from unicellular organisms.

15. The process according to claim 14, wherein the unicellular organisms are yeasts.

16. (Amended) The process according to claim 11, wherein said enzymatic mismatch repair system of said eukaryotic cells are rendered defective by genetically or physiologically manipulating said eukaryotic cells to delete or make defective at least one eukaryotic homologue of *mutS* protein and/or at least one eukaryotic homologue of *mutL* protein.

17. (Amended) The process according to claim 16, wherein said enzymatic mismatch repair system of said eukaryotic cells are rendered defective by genetically or physiologically manipulating said eukaryotic cells to delete or make defective at least one eukaryotic homologue of *mutS* protein.

18. (Amended) The process according to claim 11, wherein said enzymatic mismatch repair system of said eukaryotic cells are rendered defective by genetically or physiologically manipulated said eukaryotic cells to delete or make defective *MLH* genes, said eukaryotic cells being derived from yeast.

19. The process according to claim 11, wherein said eukaryotic cells are derived from plants.

20. The process according to claim 15, wherein said eukaryotic cells are *pms1* mutants or *msh2* mutants or *pms1 msh2* double mutants.

21. The process according to claim 11, wherein said eukaryotic cells are germ-line cells.

22. (Amended) A process of making eukaryotic cells of a hybrid eukaryotic specie, said process comprising:

mixing (a) a first group of eukaryotic cells (i) comprising a first DNA sequence and (ii) having a defective enzymatic mismatch repair system which is made defective by genetic or physiological manipulation, with (b) a second group of eukaryotic cells (i) comprising a second DNA sequence which is partially homologous to said first DNA sequence and which has up to 30% base mismatches with said first DNA sequence, and (ii) having a defective enzymatic mismatch repair system which is made defective by genetic or physiological manipulation, to form diploids,

culturing the mixture under conditions to effect meiotic recombination *in vivo* of said partially homologous first and second DNA sequences to make eukaryotic cells of said hybrid eukaryotic specie, and

recovering eukaryotic cells of said hybrid eukaryotic specie.

Kindly add the following new claims.

23. A process of making eukaryotic cells of a hybrid eukaryotic specie, said process comprising

genetically or physiologically manipulating eukaryotic cells to render defective the enzymatic mismatch repair system of said eukaryotic cells, said eukaryotic cells comprising partially homologous DNA sequences having up to 30% of base mismatches, and

culturing said manipulated eukaryotic cells under conditions to effect meiotic recombination *in vivo* of said partially homologous DNA sequences of said eukaryotic cells to thereby make eukaryotic cells of said hybrid eukaryotic specie, and

recovering eukaryotic cells of said hybrid eukaryotic specie.

24. A process of obtaining hybrid DNA sequences comprising

making eukaryotic cells of a hybrid eukaryotic specie according to the process of claim 23, and

isolating hybrid DNA sequences of said eukaryotic cells of said hybrid eukaryotic specie.

25. The process according to claim 24, wherein said hybrid DNA sequences comprise a gene.

26. A process of obtaining proteins encoded by hybrid DNA sequences comprising obtaining hybrid DNA sequences according to the process of claim 24, and expressing proteins encoded by said hybrid DNA sequences.

27. The process according to claim 26, wherein said hybrid DNA sequences comprise a gene.

28. The process according to claim 23, wherein said eukaryotic cells are derived from unicellular organisms.

29. The process according to claim 28, wherein the unicellular organisms are yeasts.

30. The process according to claim 23, wherein said enzymatic mismatch repair system of said eukaryotic cells are rendered defective by genetically or physiologically manipulating said eukaryotic cells to delete or make defective at least one eukaryotic homologue of *mutS* protein and/or at least one eukaryotic homologue of *mutL* protein.

31. The process according to claim 30, wherein said enzymatic mismatch repair system of said eukaryotic cells are rendered defective by genetically or physiologically manipulating said eukaryotic cells to delete or make defective at least one eukaryotic homologue of *mutS* protein.

32. The process according to claim 23, wherein said enzymatic mismatch repair system of said eukaryotic cells are rendered defective by genetically or physiologically manipulated said eukaryotic cells to delete or make defective *MLH* genes, said eukaryotic cells being derived from yeast.

33. The process according to claim 23, wherein said eukaryotic cells are derived from plants.

34. The process according to claim 29, wherein said eukaryotic cells are *pms1* mutants or *msh2* mutants or *pms1 msh2* double mutants.

35. The process according to claim 23, wherein said eukaryotic cells are germ-line cells.